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SERIAL NUMBER	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO
07/977,702	11/13/92	PAPAYANNOPOULOU	T 92.678

EXAMINER
TENG, S

18M1/0629

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ART UNIT	PAPER NUMBER
1812	7

DATE MAILED: 06/29/93

This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

☒ This application has been examined ☐ Responsive to communication filed on _____ ☐ This action is made final.

A shortened stetutory period for response to this action is set to expire 3 month(s), 0 days from the dete of this letter. Failure to respond within the period for response will cause the application to become abandoned. 35 U.S.C. 133

Part I THE FOLLOWING ATTACHMENT(S) ARE PART OF THIS ACTION:

1. ☐ Notice of References Cited by Examiner, PTO-892.
2. ☒ Notice re Petent Drawing, PTO-948.
3. ☒ Notice of Art Cited by Applicant, PTO-1449.
4. ☐ Notice of Informel Petent Application, Form PTO-152.
5. ☐ Information on How to Effect Drawing Changes, PTO-1474.
6. ☐ _____

Part II SUMMARY OF ACTION

1. ☒ Claims 1-14 are pending in the application
   Of the above, claims _____ are withdrawn from consideration.
2. ☐ Claims _____ have been cancelled.
3. ☐ Claims _____ are allowed.
4. ☒ Claims 1-14 are rejected.
5. ☐ Claims _____ are objected to.
6. ☐ Claims _____ are subject to restriction or election requirement.
7. ☒ This application has been filed with informal drawings under 37 C.F.R. 1.85 which are acceptable for examination purposes.
8. ☐ Formal drawings are required in response to this Office action.
9. ☐ The corrected or substitute drawings have been received on _____. Under 37 C.F.R. 1.84 these drawings are ☐ acceptable. ☐ not acceptable (see explanation or Notice re Petent Drawing, PTO-948).
10. ☐ The proposed additional or substitute sheet(s) of drawings, filed on _____ has (have) been ☐ approved by the examiner. ☐ disapproved by the examiner (see explanation).
11. ☐ The proposed drawing correction, filed on _____, has been ☐ approved. ☐ disapproved (see explanation).
12. ☐ Acknowledgment is made of the claim for priority under U.S.C. 119. The certified copy has ☐ been received ☐ not been received ☐ been filed in parent application, serial no. _____; filed on _____.
13. ☐ Since this application appears to be in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under Ex parte Queyle, 1935 C.D. 11; 453 O.G. 213.
14. ☐ Other

1. A statement that the content of the paper and computer readable copies for the sequence listing are the same should be submitted (see 37 C.F.R. 1.821(f)).

2. Claims 1-14 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

In order to avoid possible confusion over proteins with the same or similar names and abbreviations that may be found to have patentably different structure and/or utility, the names of the proteins should be written out rather than abbreviated, i.e. VLA-4, VCAM-1, G-CSF, IL-1...

Claim 1 is indefinite and incomplete because a method claim should set forth the various method steps in a positive sequential manner. It is not known as to what is involved in "peripheralizing $CD34^+$ cells", and the specification does not provide a clear definition for the term, "peripheralization".

In claim 2, the list of blocking agents is confusing. Inserting a semicolon before "fibronectin" and "soluble VCAM-1" would distinctly point out that there are three types of blocking agents. It is also not clear whether the Fab fragments or any anti-VLA-4 antibody is chimeric or humanized.

In claim 3, the phrase, "at least a portion of the $CD34^+$ cells are hematopoietic stem cells", is vague and indefinite. It is unclear as to what percentage of must be hematopoietic stem cells in order for peripheralization to proceed efficiently.

3. Claims 1-14 are rejected under 35 U.S.C. § 112, first paragraph, as the disclosure is enabling only for claims limited to the blocking agent, anti-VLA-4 antibody and the cytokine, GM-CSF. See M.P.E.P. §§ 706.03(n) and 706.03(z).

The specification does not adequately teach peripheralizing $CD34^+$ cells using fibronectin, soluble VCAM-1, Fab fragments of the anti-VLA-4 antibody, or peptides and variants thereof. Although these blocking agents are known to interfere with binding of $CD34^+$ cells to the stromal cells in vitro, applicant has not shown that these agents are capable of blocking VLA-4 antigen and peripheralizing $CD34^+$ cells in vivo. While data from in vitro assays are useful in screening for potentially useful agents, one cannot simply extrapolate the data to an in vivo system. The success of the claimed method is dependent on adequate concentrations of the agent reaching the desired site in vitro. There are many properties of these agents such as half-life, deactivation by the liver, rapid excretion, adverse side effects, etc. that cannot be ascertained by in vitro experiments.

Likewise, applicant has not provided evidence that other

cytokines can peripheralize $CD34^+$ cells in vivo. Though G-CSF is successful in peripheralizing $CD34^+$ cells in vivo, it is not known whether the other cytokines are suitable for in vivo use for reasons previously discussed.

Thus, it would require undue experimentation of one of ordinary skill in the art to use the embodiments of the invention as claimed.

4. The following is a quotation of 35 U.S.C. § 103 which forms the basis for all obviousness rejections set forth in this Office action:

> A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.
>
> Subject matter developed by another person, which qualifies as prior art only under subsection (f) or (g) of section 102 of this title, shall not preclude patentability under this section where the subject matter and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person.

Claims 1-14 are rejected under 35 U.S.C. § 103 as being unpatentable over Haas et al. or Craig et al. in view of Anklesaria et al. or Williams et al. Haas et al. teach that GM-CSF increases the number of circulating hematopoietic progenitor cells in peripheral blood (see abstract) for successful

autologous transplantation of peripheral blood stem cells. Craig et al. teach the use of GM-CSF, IL-3, or SCF to increase the number of circulating progenitor cells in peripheral blood (see page 61). However, neither Haas et al. nor Craig et al. teach the peripheralization of $CD34^+$ cells by blocking VLA-4 antigen with ligands. Anklesaria et al., or Williams et al. teach that the adhesion of the $CD34^+$ progenitor cells to bone marrow stromal cells is mediated by VLA-4/VCAM or fibronectin. Anklesaria et al. teach the use of VLA-4 ligands, such as VCAM, the CS-1 peptide (an alternatively spliced non-type III connecting segment of fibronectin), and antibodies to VLA-4, to block the adhesion of $CD34^+$ cells to stroma. Williams et al. teach that monoclonal antibodies against the α_4 subunit of VLA-4 block adhesion of CFU-S_{12} stem cells to the C terminal fibronectin fragment (containing the CS-1 site) and polyclonal antibodies against the integrin β_1 subunit inhibit the formation of CFU-S_{12} derived spleen colonies and medullary hematopoiesis (see abstract). Since, during hematopoiesis, cells are confined to the bone marrow until released into the peripheral blood, it would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the stem cell mobilization procedure taught by Haas et al. or Craig et al. by blocking the VLA-4 antigen on $CD34^+$ cells with a ligand to inhibit the adhesion of the hematopoietic stem cells to the

stroma cells and to induce their release into the peripheral blood, as taught by Anklesaria et al. or Williams et al., in order to more effectively increase the number of circulating hematopoietic stem cells for peripheral blood stem cell transplantation.

Cytokines are known to stimulate proliferation of stem cells and increase the number of circulating stem cells in peripheral blood; therefore, it would have been obvious to the skilled artisan to enhance mobilization of stem cells by using a blocking agent in combination with a cytokine. Since cytokines increase the number of $CD34^+$ and blocking agents induce release of these cells into the peripheral blood, it would have been obvious to administer the cytokine before the addition of the blocking agent. Likewise, the use of any cytokine to stimulate proliferation of hematopoietic stem cells is obvious over the prior art.

Thus, the claims are prima facie obvious over the prior art.

5. No claims are allowed.

Any inquiry concerning this communication should be directed to Sally Teng, Ph.D., at telephone number (703) 308-4230.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Papers related to this application may be submitted to Group 180 by facsimile transmission. Papers should be faxed to Group 180 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 308-4227.

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June 21, 1993

ROBERT J. HILL, JR.
SUPERVISORY PATENT EXAMINER
GROUP 1800